REMARKS

After entry of the present amendment, claims 20-28, 32, 33, 36, 37, and 39 will be pending. These claims have been amended to even more particularly describe the recited inventions. Support for the amendment can be found throughout the specification, for example, at page 11, lines 14-17 and the Examples at pages 24-26. Claims 30 and 38 have been canceled. No new matter has been added.

The present invention is directed to orally ingestible pharmaceutical tablets containing the antipsychotic 9-hydroxyrisperidone (a pharmaceutically acceptable acid addition salt thereof, an N-oxide form thereof, or a stereochemically isomeric form thereof) as the active ingredient. The tablets also comprise about 5% to less than 80%, by weight of the tablets, of pregelatinized starch, as well as one or more viscous hydrophilic polymers. The Applicants have found that the use of pregelatinized starch, in the amounts set forth, provides tablets that release 9-hydroxyrisperidone into the gastro-intestinal tract in a controlled-release manner. Importantly, the Applicants have found that the controlled-release effect occurs irrespective of whether the patient is in a fasted or fed condition.

The claims stand rejected under 35 U.S.C. § 103 as allegedly obvious over U.S. Pat No. 5,792,477 ("Rickey") in view of U.S. Patent No. 5,824,339 ("Shimizu"). The Applicants disagree and respectfully request withdrawal of the rejection.

Three criteria are required to establish a *prima facie* case of obviousness: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art references, when combined, must teach or suggest all the claim limitations. M.P.E.P. § 2142. "To support the conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest ***the claimed invention*** or the examiner must present a convincing line of reasoning as to why the artisan would have found ***the claimed invention*** to have been obvious in light of the teachings of the references." *Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985); M.P.E.P. 2142 (emphasis added). The combination of art cited by the Office fails to result in the

claimed invention. Moreover, one of skill in the art would not have been motivated to modify the cited art to produce the claimed invention.

Rickey is directed to methods of preparing injectable microparticles. Rickey at col. 7, lines 35-37; col. 17, lines 49-54. Orally ingestible tablets are not described. Indeed, it is undisputed in the art that injectable formulations of pharmaceutical compositions are wholly different from oral formulations, due in large part to the rigorous conditions of the gastrointestinal tract. Furthermore, the microparticles prepared in Rickey are hydrophobic particles. As set forth in Rickey, a first phase is prepared comprising a polymeric binder and an active agent (*i.e.*, 9-hydroxyrisperidone) having limited water solubility. A second, aqueous phase is then prepared and then the first and second phases are combined to form an emulsion. The isolated microparticles are then washed with an aqueous solution. Rickey, col. 4, lines 35-57; col. 5, lines 29-56. If these microparticles were hydrophilic, as suggested by the Office, the described emulsions would not form, nor would the resulting microparticles be able to be successfully washed with an aqueous solution. Indeed, the preferred polymers described for use in making the microparticles (poly(glycolic acid), poly-d,l-lactic acid, poly-l-lactic acid, and copolymers thereof) are ***hydrophobic***, rather than ***hydrophilic***, as the present claims require. Rickey at col. 5, lines 33-36; *see also,* U.S. Patent No. 6,306,406, claim 1.

The Office cites that Rickey describes the use of hydrophilic polymers such as polyvinyl pyrrolidone and carboxymethylcellulose. The Applicants note, however, that such compounds are used only as surfactants added to the processing medium to prevent the solvent microdroplets from agglomerating and to control the size of the solvent microdroplets in the emulsion. Rickey at col. 13, lines 60-67. Rickey does not describe that these compounds become integrated within the isolated microparticles. The Office acknowledges that pregelatinized starch limitation of the claimed invention is not mentioned in Rickey.

Shimazu is used by the Office for the "pregelatinized starch" limitation of the present invention. Shimazu is directed to the preparation of compositions that effervesce when dispersed in water. The resulting solution, not the composition alone, is then ingested. *See* Shimazu Abstract. 9-Hydroxyrisperidone is not included within the list of useful active substances. Shimazu at col. 5, lines 10-58. Moreover, Shimazu only describes "pregelatinized starch" as a binder potentially useful for "increas[ing] the strength of the

core-shell powders." Shimazu at col. 6, lines 36-46. Pregelatinized starch is noticeably absent from any of the working examples. Shimazu does not teach or suggest that pregelatinized starch is useful for producing a controlled-release effect in the gastrointestinal tract.

In order to establish a *prima facie* case of obviousness, the combination of cited art *must* result in the claimed invention. The combination of the injectable microparticles of Rickey and the effervescent compositions of Shimazu would not result in the orally ingestable tablets of the present invention. Moreover, one of skill in the art would not be motivated to modify the cited art because the cited references are from unrelated fields of pharmaceutical formulation methodology. Rickey relates solely to the preparation of injectable formulations; Shimazu relates solely to the preparation of compounds that can be administered *via* an oral solution. Shimazu at col. 5, lines 10-13. One of skill in the art would not have been motivated to combine Rickey and Shimazu because Shimazu expressly states that the methods described therein are only useful for orally administerable compounds. Rickey only describes the preparation of an injectable formulation. Rickey at col. 7, lines 35-39.

Because the combination of cited art fails to produce the claimed invention, and further because one of skill in the art would not have been motivated to modify the cited art to produce the claimed invention, the Applicants assert that a *prima facie* case of obviousness has not been established and that the claimed invention is patentable over the cited art. Withdrawal of the rejection is respectfully requested.

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The Applicants submit that the foregoing represents a *bona fide* response to the pending Office Action and that the claims are in condition for allowance. An early Notice to that effect is earnestly solicited. If the Examiner believes that a discussion with the undersigned would facilitate prosecution, the Examiner is encouraged to call (215) 564-8918.

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/Stephanie A. Barbosa/
Stephanie A. Barbosa
Registration No. 51,430

Woodcock Washburn LLP
Cira Centre
2929 Arch Street, 12th Floor
Philadelphia, PA 19104-2891
Telephone: (215) 568-3100
Facsimile: (215) 568-3439